PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :		(11) International Publication Number: WO 88/ 00469
A61K 31/56	A1	(43) International Publication Date: 28 January 1988 (28.01.88)

(21) International Application Number: PCT/US87/01646

(22) International Filing Date: 10 July 1987 (10.07.87)

(31) Priority Application Number: 885,971

(32) Priority Date: 15 July 1986 (15.07.86)

(33) Priority Country: US

(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; 685 Third Avenue, New York, NY 10017 (US).

(72) Inventor: UPTON, G., Virginia ; 208 Hermitage Drive, Radnor, PA 19087 (US).

(74) Agents: ROUTH, John, W.; American Home Products Corporation, 685 Third Avenue, New York, NY 10017 (US) et al.

(81) Designated States: JP, KR.

Published
With international search report.

(54) Title: COMBINATION DOSAGE FORM FOR PRE-MENOPAUSAL WOMEN

(57) Abstract

A method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a pre-menopausal woman in need thereof a combination dosage form of an estrogen selected from 0.5-2.0 mg of 17-β-estradiol, 0.008-0.030 mg of ethinyl estradiol, and 0.015-0.060 mg of mestranol; and a progestogen selected from 0.025-0.100 mg of levonorgestrel, 0.010-0.070 mg of gestodene, 0.025-0.100 mg of desogestrel, 0.025-0.100 mg of 3-ketodesogestrel, and 0.085-0.35 mg of norethindrone, said combination dosage form being administered for 23-25 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle. The preferred dosage form of the invention is a combination of 1 mg of 17-β-estradiol and 0.050 or 0.075 mg of levonorgestrel. The preferred administration cycle of the invention is administration of the combination dosage form for the first 24 days of the menstrual cycle and no dosage form for the last 4 days of the menstrual cycle.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

COMBINATION DOSAGE FORM FOR PRE-MENOPAUSAL WOMEN

The subject invention provides hormonal replacement therapy and contraceptive protection for the pre-menopausal woman in need thereof. Such therapy and contraceptive protection is provided by a combination dosage form of the invention which comprises a low dose of an estrogen combined with a very low dose of a progestogen. A preferred combination dosage form of the invention comprises 0.5-2.0 mg. of 17-β-estradiol and 0.025-0.100 mg. of levonorgestrel. The combination dosage form of the invention is administered for the first 23-26 days of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle. The preferred administration cycle is 24 days of the combination dosage form and 4 days of no dosage form.

Background of the Invention

Pre-menopause is defined as the time around 40 years of age when a woman can reasonably be said to be approaching menopause (the last menstrual period) or the time when a woman feels the approach of menopause by experiencing pre-menopausal irregularities in her menstrual cycle or other hypoestrogenic symptoms.

The woman over forty is in a transitional period in which her hormone levels are waning; she still ovulates and yet she experiences many of the symptoms of the hypoestrogenic woman, insomnia, hot flashes, irritability, etc. The fact that these women are still menstruating has led to the uninformed attitude that her complaints are psychosomatic in origin.

The climacteric is marked by many changes due to the natural aging process; all of which are modified by individual life-styles. Both natural and surgical menopause appear to be associated with adverse changes in metabolic parameters and in hormone levels. For example, the metabolic change in the blood lipid profile of the post-menopausal woman may lead to the development of atherselerosis, hypertension and coronary heart disease. See Notelovitz M, Graig SK, Rappaport V, et al; "Menopausal status associated with increased inhibition of blood coagulation," Am J Obstet Gynecol 141:149, (1981); Notelovitz M, Greig HBW, "Natural estrogen and anti-thrombin III activity in

postmenopausal women," J Reprod Med 16:87 (1976); Nielsen FH, Honore E, Kristoffersen K, et al, "Changes in serum lipids during treatment with norgestrel, estradiol-valerate and cycloprogynon.R Acta Obstet Gynecol Scand 56:367 (1977) and Paterson MEL, Sturdee DW, Moore B, "The effect of various regimens of hormone therapy on serum cholesterol and triglyceride concentrations in postmenopausal women," Br J Obstet Gynecol 87:552 (1980). Adverse changes in hormonal levels of the post-menopausal woman are associated with endometrial and breast cancer and with osteoporosis. See Gambrell RD Jr, Bagnell CA, Greenblatt RB, "Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: Review," Am J Obstet Gynecol 146:696 (1983); Gambrell RD Jr, "The prevention of endometrial cancer in postmenopausal women with progestogen,". Maturitas 1:107 (1978); and Nachtigall LE, Nachtigall RH, Nachtigall RD, et al, "Estrogen replacement therapy: I. A 10-year prospective study in the relationship to osteoporosis," Obstet Gynecol 53:277, (1979).

The years after 40 witness an ever-increasing number of anovulatory cycles, leaving a woman still menstruating but exposed to variable periods of unopposed estrogen. It is impossible to predict which cycles will be ovulatory or anovulatory because of the absence of any consistent pattern. Thus, the pre-menopausal woman also needs constant contraceptive protection. If one considers the the mortality rate in the aging woman due to late-childbirth, this contraceptive need becomes of paramount importance. Therefore, in consideration of the appropriate hormone therapy for the pre-menopausal woman, attention must be focused on the effects of such therapy on metabolic parameters as well as on reproductive target organs. In the pre-menopausal woman it is necessary that such therapy also be contraceptive.

Detailed Description of the Invention

In a first aspect, this invention constitutes a method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a pre-menopausal woman in need tnereof a combination dosage form of an estrogen selected from

0.5-2.0 mg. of 17-β-estradiol,

0.008-0.030 mg of ethinyl estradiol, and

0.015-0.060 mg of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,

0.010-0.70 mg. of gestodene,

0.025-0.100 mg. of desogestrel,

0.025-0.100 mg. of 3-ketodesogestrel, and

0.085-0.35 mg. of norethindrone,

said combination dosage form being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

In a second aspect, this invention provides a combination dosage form for hormonal replacement therapy and contraception for a pre-menopausal woman, comprising a combination of an estrogen slected from

0.5-2.0 mg. of 17-β-estradiol,

0.008-0.030 mg of ethinyl estradiol, and

0.015-0.060 mg of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,

0.010-0.070 mg. of gestodene,

0.025-0.100 mg. of desogestrel, and

0.025-0.100 mg. of 3-ketodesogestrel, and

0.085-0.35 mg. of norethindrone,

said combination dosage form being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

For both aspects of the invention the preferred estrogen is 17-β-estradiol and the preferred progestogen is levonorgestrel. For both aspects of the invention a preferred dosage range of the estrogen component is:

0.75-1.50 mg. of 17-β-estradiol,

0.012-0.025 mg. of ethinyl estradiol, and

0.025-0.050 mg. of mestranol; and

a preferred dosage range of the progestogen component is:

0.035-0.085 mg. of levonorgestrel,

0.015-0.060 mg. of gestodene,

0.035-0.085 mg. of desogestrel,

0.035-0.085 mg. of 3-ketodesogestrel, and

0.10-0.30 mg. of norethindrone

For both aspects of the invention the preferred estrogens are 17-β-estradiol, ethinyl estradiol and mestranol; and the preferred progestogens are levonorgestrel, gestodene, desogestrel and 3-ketodesogestrel. 17-β-estradiol and levonorgestrel are particularly preferred. Gestodene is also a particularly preferred progestogen. A particularly preferred combination dosage form for both aspects of the invention is a combination in which the estrogen is in a dose of 1 mg. of 17-β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of

gestodene, desogestrel or 3-ketodesogestrel. A further particularly preferred combination dosage form for both aspects of the invention is a combination in which the estrogen is in a dose of 1 mg. of 17-β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel, or 3-ketodesogestrel. A preferred course of administration for both aspects of the invention is administration of the combination dosage form of the invention for the first 24 days of the menstrual cycle and no dosage form (i.e., pill-free) or a blank dosage form for the last 4 days of the menstrual cycle. A further preferred course of administration for both aspects of the invention is administration of the combination dosage form for the first 23 days of the menstrual cycle and no dosage form (i.e. pill-free) or a blank dosage form for the last 5 days of the menstrual cycle. The preferred doses equivalent to 1 mg. of 17-β-estradiol are, approximately: ethinyl estradiol 0.015 mg and mestranol 0.030 mg. The preferred doses equivalent to 0.050 mg. of levonorgestrel are approximately: gestodene 0.035 mg., desogestrel and 3-ketodesogestrel 0.050 mg., and norethindrone 0.175 mg. The preferred doses equivalent to 0.075 mg. of levonorgestrel are, approximately: gestodene 0.052 mg., desogestrel and 3-ketodesogestrel 0.075 mg., and norethindrone 0.25 mg. Such equivalent doses may vary depending upon the physiological effect desired and the assay method used.

An especially preferred method of the invention comprises administering to a pre-menopausal woman in need thereof a combination dosage form of 1 mg. of 17-β-estradiol and 0.050 mg. of levonorgestrel or 1 mg. of 17-β-estradiol and 0.075 mg. of levonorgestrel for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank-pill days, for a total of 28 days in the administration cycle. An especially preferred combination dosage

form of the invention for providing hormonal replacement therapy and contraception for a pre-menopausal woman comprises a combination dosage form of 1 mg. of 17-β-estradiol and 0.050 mg. of levonorgestrel or 1 mg. of 17-β-estradiol and 0.075 mg. of levonorgestrel, said combination dosage form being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank-pill days, for a total of 28 days in the administration cycle. For both the especially preferred method and combination dosage form of the invention, the preferred cycle of administration is administration of the combination dosage form for the first 24 days of the menstrual cycle and administration of no dosage form or a blank dosage form for the last 4 days of the menstrual cycle. Or, administration of the combination dosage form for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form for the last 5 days is also preferred. A preferred dose of ethinyl estradiol equivalent to the preferred dose of 1 mg. of 17-β-estradiol is 0.015 mg. The equivalent preferred dose of mestranol is 0.030 mg. The preferred equivalent doses of desogestrel and 3-ketodesogestrel which are equivalent to the preferred doses of levonorgestrel, namely, 0.050 mg. and 0.075 mg, are also 0.050 mg. and 0.075 mg. The equivalent preferred doses of gestodene to 0.050 mg. and 0.075 mg. of levonorgestrel are 0.035 mg. and 0.052 mg. Norgestrel may be used in place of levonorgestrel, but at twice the stated dose of levonorgestrel. Levonorgestrel is particularly preferred however.

The progestogen levonorgestrel is well known and has been marketed in oral contraceptive formulations (at doses of 0.15 mg. and higher) for many years. Its chemical name is (-)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one. Norgestrel's common name is 17-α-ethynyl-18-homo-19-nortestosterone. Gestodene, desogestrel, and 3-ketodesogestrel are newer progestogens in

various stages of clinical development and use. The new compound, gestodene, differs from norgestrel by a double bond in the 15 position and is progestationally active per se, whereas desogestrel is inactive as the parent molecule and must undergo two metabolic steps for progestational activity. Desogestrel is metabolized first to the biologically active 3β-hydroxydesogestrel with estrogenic/-androgenic activity and then to 3-ketodesogestrel, which has progestogenic activity; it differs from norgestrel by a methylene group at position 11. Norethindrone's chemical name is 17-hydroxy-19-norpregn-4-en-20-yn-3-one. It is also known as 19-northisterone or northisterone. Norethindrone acetate may be used in place of norethindrone.

17-β-estradiol is the most potent naturally occurring estrogen in mammals. Its chemical name is estra-1,3,5(10)-triene-3,17-diol. 17-β-estradiol (or β-estradiol) is its common name. Ethinyl estradiol and mestranol are both synthetic estrogens which have an ethinyl group at the 17 position of the estradiol ring structure. Mestranol additionally has a methoxy group rather than a hydroxy group at the 3 position of the estradiol ring structure. Ethinyl estradiol and mestranol are used in oral contraceptive-formulations. The composition of such marketed oral contraceptives is shown in Table 15-2 on page 454 in Chapter 15 "Fertility Control and its Complications" by Bruce R. Carr and James E. Griffin in Williams Textbook of Endocrinology, seventh edition, (Jean D. Wilson M.D. and Daniel W. Foster, M.D. (W.B. Saunders Company, Philadelphia, 1985).

The combination dosage form utilized in both the method of treatment and dosage form aspects of the invention may conveniently be administered by providing the patent with a blister pack type product as is commonly used with oral contraceptive products. Such product would normally comprise the

appropriate number of dosage tablets in a sealed blister pack in a cardboard, paperboard or plastic sleeve with a protective cover or box. Each combination dosage tablet blister container would be numbered or otherwise marked for the first 23-26 days of the menstrual cycle, as prescribed by the patient's physician. The remaining 2-5 (pill-free) days of the 28 day administration cycle would contain blank-pills or unfilled blisters or other marking devices to assist the patient in following the prescribed administration cycle. The combination estrogen and progestogen dosage form of the invention is preferrably provided as a tablet, caplet or capsule in a manner known in the art. Other oral or parenteral dosage preparations or packages may be provided as known in the art.

In the Claims:

1. A method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a pre-menopausal woman in need thereof a combination dosage form of an estrogen selected from

0.5-2.0 mg. of 17-β-estradiol,

0.008-0.030 mg of ethinyl estradiol, and

0.015-0.060 mg of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,

0.010-0.070 mg. of gestodene,

0.025-0.100 mg. of desogestrel,

0.025-0.100 mg. of 3-ketodesogestrel, and

0.085-0.35 mg. of norethindrone,

said combination dosage form being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

2. A method according to Claim 1 in which the estrogen selected is 17-β-estradiol.

3. A method according to Claim 1 in which the progestogen selected is levonorgestrel.

4. A method according to Claim 1 in which the progestogen is selected from levonorgestrel, gestodene, desogestrel and 3-ketodesogestrel.

5. A method according to Claim 1 in which the combination dosage form has an estrogen selected from:

0.75-1.50 mg. of 17-β-estradiol,

0.012-0.025 mg. of ethinyl estradiol, and

0.025-0.050 mg. of mestranol; and

a progestrogen selected from:

0.035-0.085 mg. of levonorgestrel,

0.015-0.060 mg. of gestodene,

0.035-0.085 mg. of desogestrel,

0.035-0.085 mg. of 3-ketodesogestrel, and

0.10-0.30 mg. of norethindrone

6. A method according to Claim 1 in which the estrogen is in a dose of 1 mg. of 17-β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

7. A method according to Claim 1 in which the estrogen is in a dose of 1 mg. of 17-β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

8. A method according to Claim 1 in which the combination dosage form is administered for the first 24 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 4 days of menstrual cycle.

9. A method according to Claim 1 in which the combination dosage form is administered for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 5 days of the menstrual cycle.

10. A method of providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises administering to a

pre-menopausal woman in need thereof a combination dosage form of 1 mg. of 17-β-estradiol and 0.050 mg. of levonorgestrel or 1 mg. of 17-β-estradiol and 0.075 mg. of levonorgestrel for 23-26 days beginning at day one of the menstrual cycle, followed by a 2-5 pill-free or blank pill days for a total of 28 days in the administration cycle.

11. A method according to Claim 7 in which the combination dosage form is administered for the first 24 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 4 days of the menstrual cycle.

12. A method according to Claim 1 in which the combination dosage form is administered for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 5 days of menstrual cycle.

13. A combination dosage form for hormonal replacement therapy and contraception for a pre-menopausal woman, comprising a combination of an estrogen selected from

0.5-2.0 mg. of 17-β-estradiol,

0.010-0.030 mg of ethinyl estradiol, and

0.015-0.060 mg of mestranol;

and a progestogen selected from

0.025-0.100 mg. of levonorgestrel,

0.010-0.070 mg. of gestodene,

0.025-0.100 mg. of desogestrel,

0.025-0.100 mg. of 3-ketodesogestrel, and

0.085-0.35 mg. of norethindrone,

said combination dosage form being administered for 23-25 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days, for a total of 28 days in the administration cycle.

14. A combination dosage form according to Claim 13 in which the estrogen selected is 17-β-estradiol.

15. A combination dosage form according to Claim 13 in which the progestogen selected is levonorgestrel.

16. A combination dosage form according to Claim 13 in which the estrogen is selected from:

0.75-1.50 mg. of 17-β-estradiol,

0.012-0.025 mg. of ethinyl estradiol, and

0.025-0.050 mg. of mestranol; and

a progestogen selected from:

0.035-0.085 mg. of levonorgestrel,

0.015-0.060 mg. of gestodene,

0.035-0.085 mg. of desogestrel,

0.035-0.085 mg. of 3-ketodesogestrel, and

0.10-0.30 mg. of norethindrone,

17. A combination form according to Claim 13 in which the estrogen is in a dose of 1 mg. of 17-β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.050 mg. of levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

18. A combination dosage form according to Claim 13 in which the estrogen is in a dose of 1 mg. of 17-β-estradiol or an equivalent dose of ethinyl estradiol or mestranol and the progestogen is in a dose of 0.075 mg. of

levonorgestrel or an equivalent dose of gestodene, desogestrel or 3-ketodesogestrel.

19. A combination dosage form according to Claim 13 in which the combination dosage form is administered for the first 24 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 4 days of menstrual cycle.

20. A combination dosage form according to Claim 13 in which the combination dosage form is administered for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 5 days of menstrual cycle.

21. A combination dosage form for providing hormonal replacement therapy and contraception for a pre-menopausal woman, which comprises a combination dosage form of 1 mg. of 17-β-estradiol and 0.50 mg. of levonorgestrel or 1 mg. of 17-β-estradiol and .075 mg. of levonorgestrel, said combiantion being administered for 23-26 days beginning at day one of the menstrual cycle, followed by 2-5 pill-free or blank pill days of the menstrual cycle, for a total of 28 days in the administration cycle.

22. A combination dosage form according to Claim 15 in which the combination dosage form is administered for the first 24 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 4 days of the menstrual cycle.

23. A combination dosage form according to Claim 22 in which the combination dosage form is administered for the first 23 days of the menstrual cycle and no dosage form or a blank dosage form is administered for the last 5 days of the menstrual cycle.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US87/01646

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/56

U.S.Cl.: 514/170

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514/170

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	EP, 0,036,229 (DE JAGER) 23 September 1981 (23.09.81); See page 6, lines 1-25.	1-23
Y	DE, 3,347,125 A1 (SCHERING) 11 July 1985 (11.07.85); See Derwent Summary.	1-23
Y	UK, 2,096,462 (PRITCHARD) 20 October 1982 (20.10.82); See page 1, lines 85-87.	1-23
Y	N. FRANCIS, H., "Oral Contraception" Proceedings of The Royal Society of Medicine, Vol. 57; March 1964; pp. 203-207; See page 203, first paragraph.	1-23

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]

22 SEPTEMBER 1987

Date of Mailing of this International Search Report [2]

14 OCT 1987

International Searching Authority [1]

ISA/US

Signature of Authorized Officer [20]

Joseph Lipovsky

Joseph Lipovsky

Form PCT/ISA/210 (second sheet) (May 1986)